Cellular Mechanisms Regulating Urokinase-Type Plasminogen Activator (Upa) 
In Hormone Refractory Prostate Cancer: A Novel Therapeutic Target.

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**Background** Increased expression of the hepatocyte growth factor (HGF) receptor (c-Met) and uPA correlates with the development of high grade prostatic adenocarcinoma (CaP) and metastasis. However, the mechanism(s) by which HGF/c-Met signaling mediate prostate cancer progression and metastasis are unclear. Data from our laboratory demonstrates that HGF/c-Met signaling upregulates uPA and stimulates invasion through Matrigel of high versus low metastatic human CaP cells. The purpose of this study was to test the action of a novel uPA-receptor antagonist (A36) and to determine its direct affects on the growth, invasion and metastasis of hormone refractory PC3MLN4 CaP cells. A36 inhibited the binding of uPA to uPAR on HeLa cells with an IC50=30 nM.

**Methods** To assess its potential anti-proliferative effects, PC3M cells growing in vitro were treated for 72 h with A36 (0–1000 nM) and HGF (40 ng/ml).

**Results** A36 did not suppress HGF-induced tumor cell proliferation versus controls. The effect of A36 on the in vitro invasiveness of PC3MLN4 CaP cell was evaluated using a matrigel two-chamber assay. A36 (0–1000 nM) inhibited HGF-induced tumor cell invasion in a dose-dependent manner. Analyses in progress are testing the effects A36 on the orthotopic growth, invasion and metastasis of PC3M LN4 CaP cell in nude mice.

**Conclusion** These studies shed light on the role of c-Met signaling and uPA activity in the growth, invasion, and metastasis of CaP cells in vitro and in vivo. Knowledge gained from this research may provide a therapeutic basis for interfering with metastases produced by hormone refractory CaP by downregulating uPA-mediated proteolysis.